a31 genetic code, and (f) a polynucleotide that represents a fragment, derivative, or allelic variation of a nucleic acid sequence specified in (a) - (e).

Remarks

The Amendments

Claims 1, 6, 11, 22, 27, 62, and 69 and the specification have been amended to insert the Accession Number of plasmid pCRII-TMSP3. The ATCC deposit information for plasmid pCRII-TMSP3 is attached.

Claims 1, 6, 11, 22, and 62 have been amended to delete the recitation of "biologically active variants." Claims 27 and 69 have been amended to delete the recitation of "a fragment, derivative, or allelic variation."

Claim 27 has been amended to recite that the polynucleotides the kit comprise "at least 225 contiguous nucleotides" in place of "at least 11 contiguous nucleotides." This amendment is supported by the specification, which discloses that "a polynucleotide sequence encoding a transmembrane serine protease polypeptide can be detected . . . using probes or fragments or fragments of polynucleotides encoding a transmembrane serine protease polypeptide" (page 24, lines 5-8) and "[t]ransmembrane serine protease polypeptides according to the invention comprise at least 10, 15, 25, 50, 75, . . . contiguous amino acids selected from SEQ ID NO: 12 or a biologically active variant thereof" (page 10, lines 9-12). Because each amino acid is encoded by a three-nucleotide codon, a polypeptide comprising at least 75 contiguous amino acids is encoded by a polynucleotide comprising at least 225 contiguous nucleotides.

Claim 27 also has been amended to recite at elements (a) and (b): "(a) a polynucleotide comprising the complete complement of the nucleotide sequence shown in SEQ ID NO:11, (b) a polynucleotide comprising the complete complement of the coding sequence of the cDNA insert of plasmid pCRII-TMSP3 (ATCC Accession No. PTA-3433)." These amendments are supported at page 13, lines 2-4 of the specification: "A transmembrane serine protease polynucleotide can be single- or double-stranded and comprises a coding sequence or the complement of a coding sequence for a transmembrane serine protease polypeptide." Claim 27 also has been amended to incorporate the recitations of canceled claim 25.

Claim 69 has been amended to recite that element (e) is "a polynucleotide which hybridizes under stringent conditions along the full length of a polynucleotide specified in (a) - (d)." This amendment is supported by the specification at page 13, lines 2-4, quoted above.

None of these amendments introduces new matter.

Objection to the Specification

The specification has been objected to because an ATCC Accession Number for plasmid pCRII-TMSP3 is mentioned throughout the specification without an indication of its specific deposit number. The specification has been amended to insert PTA-3433 as the ATCC Accession Number. Withdrawal of this objection is respectfully requested.

Objection to the Drawings

The drawings have been objected to under 37 C.F.R. § 1.84. Copies of corrected drawings are submitted with this response. Formal copies of the drawings will be filed separately. Withdrawal of this objection is respectfully requested.

Objection to Claim 69

Claim 69 has been objected to for having a semicolon inserted between "polynucleotide specified in (a)-(d)" and "(e) a polynucleotide having." Claim 69 has been amended to replace the semicolon with a comma as suggested in the Office Action. Withdrawal of this objection is respectfully requested.

The Rejection of Claims 1-15, 22-24, 27, 62-64, and 69-71 Under 35 U.S.C. § 112, second paragraph

Claims 1-15, 22-24, 27, 62-64, and 69-71 stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite. Applicants respectfully traverse.

First, the Office Action asserts that claims 1, 6, 11, 22, 27, 62, and 69 (and dependent claims 2-5, 7-10, 12-15, 23, 24, 63, 64, 70, and 71) are indefinite because they recite "ATCC Accession No. _____." Claims 1, 6, 11, 22, 27, 62, and 69 have been amended to insert "PTA-3433" as the specific ATCC deposit number.

Second, the Office Action asserts that the recitation "biologically active variants" in claims 1, 6, 11, 22, 27, and 62 (and dependent claims 2-5, 7-10, 12-15, 23, 24, 63, and 64) is indefinite. To advance prosecution, claims 1, 6, 11, 22, 27, and 62 have each been amended to delete "biologically active variants."

Third, the Office Action asserts that the recitation of "the complement" of the sequences recited in elements (a) and (b) of claim 27 is indefinite. To advance prosecution, elements (a) and (b) have been amended to recite "a polynucleotide comprising the complete complement" of the recited nucleotide sequences.

Fourth, the Office Action states that it is unclear why the phrase "to nucleic acid material of a biological sample to form a hybridization complex" has been included in claim 27, element (b). (Paper 9, page 13-14.) The phrase was inadvertently and erroneously included in claim 27 and has been deleted.

Finally, The Office Action asserts that the recitation in claims 27 and 69 of "polynucleotide that hybridizes under stringent conditions" is unclear because the conditions under which the hybridization is performed have not been stated. (Paper 9, page 5, lines 18-19.) The standard for assessing whether a patent claim is sufficiently definite to satisfy the statutory requirement is whether one skilled in the art would understand the bounds of the claim when read in light of the specification. *Miles Labs., Inc. v. Shandon, Inc.*, 997 F.2d 870 (Fed. Cir. 1993). The specification defines the meaning of "stringent conditions" as recited in claims 27 and 69:

> Typically, for stringent hybridization conditions a combination of temperature and salt concentration should be chosen that is approximately 12-20 °C below the calculated T_m of the hybrid under study. The T_m of a hybrid between a transmembrane serine protease polynucleotide having a coding sequence disclosed herein and a polynucleotide sequence which is at least about 50, 55, 60, 65, 70, preferably about 75, 90, 96, or 98% identical to that nucleotide sequence can be calculated, for example, using the equation of Bolton and McCarthy, *Proc. Natl. Acad. Sci. U.S.A. 48*, 1390 (1962):
>
> $T_m = 81.5\ °C - 16.6(\log_{10}[Na^+]) + 0.41(\%G + C) - 0.63(\%\text{formamide}) - 600/l$,
>
> where l = the length of the hybrid in basepairs.

> Stringent wash conditions include, for example, 4X SSC at 65 °C, or 50% formamide, 4X SSC at 42 °C, or 0.5X SSC, 0.1% SDS at 65 °C.

Page 14, line 22 to page 15, line 4. Thus, when read in light of the specification, one skilled in the art would understand the bounds of "stringent conditions" as recited in claims 27 and 69.

Withdrawal of these rejections to claims 1-15, 22-24, 27, 62-64, and 69-71 is respectfully requested.

The Rejection of Claims 1, 6, 11, 22, 27, 62, and 69-71 Under 35 U.S.C. § 112, first paragraph

Claims 1, 6, 11, 22, 27, 62, and 69-71 stand rejected under 35 U.S.C. § 112, first paragraph as lacking adequate written description and/or enablement. The rejections are respectfully traversed.

1. Written Description of Claims 1, 6, 11, 22, 27, 62, and 69

Claims 1, 6, 11, 22, 27, 62, and 69 are said to lack written description. Applicants respectfully traverse.

To comply with the written description requirement, the description must clearly convey to persons of ordinary skill in the art that applicants possessed the claimed subject matter when the application was filed. *Vas-Cath v. Mahurkar*, 19 U.S.P.Q.2d (BNA) 1111, 1117 (Fed. Cir. 1991). The specification meets this requirement.

Claims 1, 6, 11, 22, 27, 62, and 69 are directed to cDNAs (claim 1), expression vectors (claim 6), host cells (claim 11), methods of producing a polypeptide (claim 22), kits (claim 27), pharmaceutical compositions (claim 62), and isolated polynucleotides (claim 69). The Office Action asserts that these claims lack adequate written description because they recite a genera of

polynucleotides "of any function encoding any fragment or variant of the polypeptide of SEQ ID NO: 12 or the polypeptide encoded by the plasmid pCRII-TMSP3." (Paper 9, page 6, lines 15-17.)

To advance prosecution, claims 1, 6, 11, 22, and 62 have been amended to recite molecules that encode either (a) the amino acid sequence shown in SEQ ID NO:12 or (b) the amino acid sequence encoded by a cDNA insert contained within plasmid pCRII-TMSP3 (ATCC Accession No. PTA-3433). The specification adequately describes the subject matter of amended claims 1, 6, 11, 22, and 62.

The Office Action acknowledges that the specification discloses the polypeptide of SEQ ID NO:12 and a polynucleotide sequence encoding SEQ ID NO:12 (*i.e.*, SEQ ID NO:11). (Paper 9, page 7, lines 4-6.) Because the genetic code is widely known, disclosure of an amino acid sequence provides sufficient information such that one of skill in the art would understand that applicants possessed the full genus molecules that encode the recited amino acid sequence. *In re Bell*, 991 F.2d 781, 785 (Fed. Cir. 1993). See also MPEP § 2163 (3)(ii)(b). Thus, the specification discloses the genus of molecules that encode SEQ ID NO:12.

Reference in the specification to a deposit constitutes an adequate description of the deposited material sufficient to comply with the written description requirement. *Enzo Biochem v. Gen-Probe Incorporated*, 296 F.3d 1316, 1325 (Fed. Cir. 2002). Thus the polypeptide comprising the amino acid sequence encoded by the cDNA insert contained within plasmid pCRII-TMSP3 (ATCC Accession No. PTA-3433). Together with the genetic code, the deposit conveys to one of skill in the art that applicants possessed the genus of molecules encoding the recited polypeptide.

Amended claims 27 and 69 also meet the written description requirement. Claims 27 and 69 have been amended to delete the recitation of "a fragment, derivative, or allelic variation of a nucleic acid sequence." The polynucleotides recited in claim 27 comprise at least 225 contiguous nucleotides of (a) a polynucleotide comprising the complete complement of SEQ ID NO:11, (b) a polynucleotide comprising the complete complement of the coding sequence of the cDNA insert of plasmid pCRII-TMSP3 (ATCC Accession No. PTA-3433), (c) polynucleotides that hybridize under stringent conditions along the full-length nucleotide sequence of (a) or (b), and (d) polynucleotides having a nucleic acid sequence that deviates from the nucleotide sequence of (a) – (c) due to the degeneration of the genetic code.

The specification conveys to one of skill in the art that applicants possessed the polynucleotides recited in each of elements (a) through (d) of claim 27:

- "a polynucleotide comprising the complete complement of the nucleotide sequence shown in SEQ ID NO:11" (element (a))

The specification discloses the nucleotide sequence of SEQ ID NO:11. The rules of complementary base pairing were well-known in the art when this application was filed. By disclosing SEQ ID NO:11, the specification also discloses the sequence that is the complete complement of SEQ ID NO:11. Thus, the specification demonstrates to one of skill in the art that Applicants possessed polynucleotides comprising the complete complement of the nucleotide sequence shown in SEQ ID NO: 11.

- "a polynucleotide comprising the complete complement of the coding sequence of the cDNA insert of plasmid pCRII-TMSP3 (ATCC Accession No. PTA-3433)" (element (b))

Applicants have deposited plasmid pCRII-TMSP3 (ATCC Accession No. PTA-3433). As noted above, a reference in the specification to a deposit constitutes an adequate description

of the deposited material sufficient to comply with the written description requirement. *Enzo Biochem v. Gen-Probe Incorporated*, 296 F.3d 1316, 1325 (Fed. Cir. 2002). Thus the coding sequence of the cDNA insert of plasmid pCRII-TMSP3 (ATCC Accession No. PTA-3433) is adequately described. Again, because of the complementary base pairing rules, one of skill in the art would understand that deposit of the plasmid pCRII-TMSP3 (ATCC Accession No. PTA-3433) indicated that Applicants possessed polynucleotides comprising the complete complement of the coding sequence of the cDNA insert of that plasmid.

- "a polynucleotide that hybridizes under stringent conditions along the full-length of the polynucleotides of (a) or (b)" (element (c))

As explained above, the specification conveys to one of skill in the art that applicants possessed the polynucleotides recited in (a) and (b). Stringent hybridization conditions were well-known in the art when the application was filed, and one of skill in the art would have possessed this knowledge. Moreover, the specification teaches stringent hybridization conditions at page 14, line 22 to page 15, line 4. Thus, the specification adequately conveys to one of skill in the art that applicants possessed polynucleotides that hybridize under stringent conditions along the full-length of the polynucleotides of elements (a) and (b).

- "a polynucleotide having a nucleic acid sequence that deviates from the nucleic acid sequences specified in (a) to (c) due to the degeneration of the genetic code" (element (d))

As explained above, the specification conveys to one of skill in the art that applicants possessed the polynucleotides recited in (a, (b), and (c). The degeneracies of the genetic code were well known in the art at the time the application was filed, and one of skill in the art would have possessed this knowledge. Thus, one of skill in the art would have recognized that

applicants possessed polynucleotides that have a nucleic acid sequence that deviates from the nucleic acid sequences specified in (a) to (c) due to the degeneration of the genetic code.

The specification also adequately describes each of the molecules recited in elements (a) through (f) of claim 69.

- a polynucleotide that encodes a protein that comprises the amino acid sequence of SEQ ID NO:12 (element (a))

The Office Action acknowledges that the specification discloses the polypeptide of SEQ ID NO:12 and a polynucleotide that encodes it. (Paper 9, page 7, lines 4-6.) Because the genetic code is widely known, disclosure of an amino acid sequence provides sufficient information such that one of skill in the art would understand that applicants possessed the full genus molecules that encode the recited amino acid sequence. *In re Bell*, 991 F.2d 781, 785 (Fed. Cir. 1993). See also MPEP § 2163 (3)(ii)(b). Thus, the specification adequately describes the genus of molecules that encode SEQ ID NO:12.

- a polynucleotide that comprises the polynucleotide of SEQ ID NO:11 (element (b))

The specification discloses the nucleotide sequence of SEQ ID NO:11, demonstrating that Applicants possessed polynucleotides that comprise this nucleotide sequence.

- a polynucleotide that comprises the coding sequence of a cDNA contained within plasmid pCRII-TMSP3 (ATCC Accession No. PTA-3433 (element (c))

Plasmid pCRII-TMSP3 has been deposited as ATCC Accession No. PTA-3433. A reference in the specification to a deposit constitutes an adequate description of the deposited material sufficient to comply with the written description requirement. *Enzo Biochem v. Gen-Probe Incorporated*, 296 F.3d 1316, 1325 (Fed. Cir. 2002). Thus, Applicants had possession of

polynucleotides comprising the coding sequence of the cDNA insert contained within plasmid pCRII-TMSP3 (ATCC Accession No. PTA-3433).

- a polynucleotide that encodes a protein that comprises the amino acid sequence encoded by the cDNA of pCRII-TMSP3 (ATCC Accession No. PTA-3433 (element (d))

Plasmid pCRII-TMSP3 has been deposited as ATCC Accession No. PTA-3433. A reference in the specification to a deposit constitutes an adequate description of the deposited material sufficient to comply with the written description requirement. *Enzo Biochem v. Gen-Probe Incorporated*, 296 F.3d 1316, 1325 (Fed. Cir. 2002). Together with the genetic code, the deposit adequately conveys to one of skill in the art that applicants possessed the genus of molecules encoding the polypeptide is adequately described.

- polynucleotides that hybridize under stringent conditions along the full-length of the polynucleotides specified in (a) – (d) (element (e))

As explained above, the specification conveys to one of skill in the art that applicants possessed the polynucleotides recited in (a) - (d). Stringent hybridization conditions were well-known in the art when the application was filed, and one of skill in the art would have possessed this knowledge. Moreover, the specification teaches stringent hybridization conditions at page 14, line 22 to page 15, line 4. Thus, the specification adequately conveys to one of skill in the art that applicants possessed polynucleotides that hybridize under stringent conditions along the full-length of the polynucleotides of elements (a) - (d).

- polynucleotides that have a nucleic acid sequence that deviates from the nucleic acid sequences specified in (a) – (e) due to the degeneracy of the genetic code (element (f))

As explained above, the specification conveys to one of skill in the art that applicants possessed the polynucleotides recited in (a) - (e). The degeneracies of the genetic code were

well known in the art at the time the application was filed, and one of skill in the art would have possessed this knowledge. Thus, one of skill in the art would have recognized that applicants possessed polynucleotides that have a nucleic acid sequence that deviates from the nucleic acid sequences specified in (a) to (e) due to the degeneration of the genetic code.

The specification, together with knowledge well-known in the art at the time of filing, conveys to one of skill in the art that applicants possessed the subject matter of claims 1, 6, 11, 22, 27, 62, and 69. Withdrawal of this rejection is respectfully requested.

2. Enablement of Claims 1, 6, 11, 22, 27, 62, and 69-71

Claims 1, 6, 11, 22, 27, 62, and 69-71 are rejected as not enabled. Applicants respectfully traverse.

To satisfy the enablement requirement, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557 (Fed. Cir. 1993). That some experimentation may be required is not fatal; the issue is whether the amount of experimentation required is "undue." *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). The present specification teaches those of skill in the art how to make and use the invention of claims 1, 6, 11, 22, 27, 62, and 69-71 without the need for undue experimentation.

The Office Action asserts that claims 1, 6, 11, 22, 27, 62, and 69-71 are not enabled because:

> While Applicants have disclosed the function and structure of the polypeptide of SEQ ID NO:12 and the structure of the corresponding polynucleotide (SEQ ID NO:11), no disclosure of the function of the polynucleotides encompassed by the claims has been provided. The specification does not provide any information as to which structural elements are related to transmembrane serine

> protease activity or the structural elements a polynucleotide as encompassed by the claims should have to display serine protease activity.

Paper 9, page 9, lines 4-11.

Claims 1, 6, 11, 22, and 62

Claims 1, 6, 11, 22, and, 62 have been amended to delete the recitation of "biologically active variants." Claims 1, 6, 11, 22, and 62 now recite molecules that encode a polypeptide comprising either (a) an amino acid sequence as shown in SEQ ID NO: 12 or (b) the amino acid sequence encoded by a cDNA insert contained within plasmid pCRII-TMSP3 (ATCC Accession No. PTA-3433). The Office Action acknowledges that these molecules are enabled. (Paper 9, page 8, lines 10-12.) Thus amended claims 1, 6, 11, 22, and 62 are enabled.

Claim 27

Claim 27 also is enabled. Claim 27 is directed to a kit for detecting a coding sequence for a polypeptide comprising an amino acid sequence as shown in SEQ ID NO:12 or a polypeptide encoded by a cDNA insert contained within plasmid pCRII-TMSP3 (ATCC Accession No. PTA-3433). The kit comprises a polynucleotide comprising at least 225 contiguous nucleotides of (a) a polynucleotide comprising the complete complement of the nucleotide sequence shown in SEQ ID NO: 11, (b) a polynucleotide comprising the complete complement of the coding sequence of the cDNA insert of plasmid pCRII-TMSP3 (ATCC Accession No. PTA-3433), (c) a polynucleotide that hybridizes under stringent conditions along the full-length nucleotide sequence of (a) or (b), and (d) a polynucleotide having a nucleic acid sequence that deviates form the nucleic acid sequences specified in (a) to(c) due to the

degeneration of the genetic code. One of skill in the art could make and use each of these molecules without having to resort to undue experimentation.

First, it would not require undue experimentation for one of skill in the art to make and use a polynucleotide molecule comprising either at least 225 contiguous nucleotides of a polynucleotide comprising the complete complement of the nucleotide sequence of SEQ ID NO: 11 (element (a) of claim 27) or the complete complement of the coding sequence of the cDNA insert of plasmid pCRII-TMSP3 (ATCC Accession No. PTA-3433) (element (b) of claim 27). The specification discloses the nucleotide sequence of SEQ ID NO: 11. Applicants deposited plasmid pCRII-TMSP3 (ATCC Accession No. PTA-3433) under the provisions of the Budapest Treaty, making the plasmid publicly available. The rules of complementary base pairing were well known in the art prior to the filing of the application. Thus it would not have required undue experimentation for one of skill in the art to make and use polynucleotides comprising at least 225 polynucleotides selected from the complements of these molecules.

Polynucleotides having a sequence that hybridizes to the polynucleotides recited in either element (a) or element (b) (*i.e.*, element (c) of claim 27) also are enabled. As demonstrated above, the polynucleotides recited in (a) and (b) are disclosed and enabled. The specification defines "stringent hybridization conditions" at page 14, line 22 to page 15, line 4. Provided with the disclosure of the polynucleotide molecules recited in (a) and (b), the definition of stringent hybridization conditions in the specification, and the well-known rules of complementary base pairing, one of skill in the art could make and use the polynucleotides of element (c) without having to resort to undue experimentation.

Polynucleotides having a nucleic acid sequence that deviates from the nucleic acid sequences specified in (a) to(c) due to the degeneration of the genetic code (*i.e.*, element (d) of claim 27) also are enabled. The polynucleotide molecules of elements (a) to (c) are disclosed and enabled. The degeneracies of the genetic code were well known in the art when the application was filed. Together with the disclosures of the molecules of elements (a) – (e) and the degeneracy of the genetic code, one of skill in the art could easily make and use the molecules recited in element (d) of claim 27 without having to resort to undue experimentation.

Claims 69-71

Independent claim 69 is directed to an isolated polynucleotide. The polynucleotide is either (a) a polynucleotide encoding a protein that comprises the amino acid sequence of SEQ ID NO: 12, (b) a polynucleotide comprising the sequence of SEQ ID NO 11, (c) a polynucleotide comprising a coding sequence of a cDNA contained within plasmid pCRII-TMSP3 (ATCC Accession No. PTA-3433), (d) a polynucleotide encoding a protein that comprises the amino acid sequence encoded by the cDNA of plasmid pCRII-TMSP3 (ATCC Accession No. PTA-3433), (e) a polynucleotide which hybridizes under stringent conditions along the full length of a polynucleotide specified in (a) – (d), or (f) a polynucleotide having a nucleic acid sequence that deviates from the nucleic acid sequence specified in (a) – (e) due to the degeneration of the genetic code. Each of these polynucleotides can be made and used by one of skill in the art without recourse to undue experimentation.

The Office Action acknowledges that the polynucleotides of elements (a) – (d) of claim 69 are enabled. (Paper 9, page 8, lines 10-12.) Polynucleotides that hybridize under stringent condition along the full length of the polynucleotides of (a) – (d) are also enabled (element (e) of

claim 27). The polynucleotides of (a) – (d) are disclosed and enabled. The specification defines "stringent hybridization conditions" on page 14, line 22 to page 15, line 4. Together with the disclosures of these molecules, the definition of stringent hybridization condition in the specification, and the will-known rules of complementary base pairing, one of skill in the art could make and use the polynucleotides of element (e) without resorting to undue experimentation.

Polynucleotides having a nucleic acid sequence that deviates from the nucleic acid sequence specified in (e) due to degeneration of the genetic code are also enabled (element (f) of claim 69). The polynucleotides of element (e) are disclosed and enabled. The degeneracies of the genetic code were well known in the art when the application was filed. Together with the disclosures of the molecules of element (e) and the degeneracies of the genetic code, one of skill in the art could easily make and use the molecules recited in element (f) without having to resort to undue experimentation.

Claims 62-64

The Office Action asserts that the specification does not reasonably provide enablement for the pharmaceutical compositions of claims 62-64. (Paper 9, page 10, lines 8-12.) The pharmaceutical compositions comprise an expression vector encoding a polypeptide that comprises an amino acid sequence selected from the group consisting of (a) the amino acid sequence shown in SEQ ID NO:12 and (b) the amino acid sequence encoded by a cDNA insert contained within plasmid pCRII-TMSP3 (ATCC Accession No. PTA-3433).

The Patent Office has failed to meet its burden of establishing a *prima facie* case of non-enablement of claims 62-64. Whenever an enablement rejection is made, the Patent Office must

explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. *In re Marzocchi*, 169 U.S.P.Q. (BNA) 367, 370 (C.C.P.A. 1971).

The Office Action asserts that claims 62-64 are not enabled because "[n]either the specification nor the prior art provide sufficient guidance as to what specific diseases could be successfully treated by administering a 'pharmaceutical composition' comprising the vectors as encompassed by the claim." (Paper 9, page 11, lines 5-8.) The specification discloses two specific categories of diseases that can be treated with the recited pharmaceutical compositions (*i.e.*, diseases in which transmembrane serine protease activity should be increased): viral infection and neurodegenerative diseases. The specification also teaches why the disclosed pharmaceutical composition would be effective to treat these disorders. With respect to viral infection, the specification teaches: "Removal of the cell surface components by transmembrane serine protease may influence the ability of viruses to attach to the cell surface. Regulation of transmembrane serine protease may therefore be used to treat viral infections." (Page 49, lines 12-15.) With respect to neurodegenerative diseases, the specification teaches: "It is also possible that transmembrane serine protease activity can be used to degrade, for example, prion protein amyloid plaques of Genstmann-Straussler Syndrome, Creutzfeldt-Jakob disease, and Scrapie." (Page 49, lines 16-18.)

In asserting that the specification provides no guidance regarding what diseases can be treated, the Patent Office merely states that the specification "merely provides a large list of diseases." (Paper 9, page 11, lines 9-11.) This assertion does not satisfy the Patent Office's burden for making a *prima facie* case of non-enablement. The Patent Office has offered no

scientific evidence or reasoning that is inconsistent with the statements in the specification that viral infection and neurodegenerative diseases can be treated.

The Office Action also asserts that the specification provides no indication of therapeutic doses. (Paper 9, page 11, lines 11-12.) On the contrary, the specification not only provides an indication of therapeutic doses but also guides one of skill in the art in determining therapeutically effective doses. See pages 55-56 ("*Determination of a therapeutically effective dose*"). The specification specifically teaches that "[n]ormal dosage amounts can vary from 0.1 to 100,000 micrograms, up to a total dose of about 1 g, depending upon the route of administration." (Page 55, lines 3-4.) Thus the specification provides an indication of therapeutic doses for the claimed pharmaceutical compositions and accordingly, one of skill in the art would not have to resort to undue experimentation to determine a therapeutic dose.

Finally, the Office Action assets that the specification provides no guidance as to what, besides the recited expression vector, would be included in a pharmaceutical composition. (Paper 9, page 11, lines 15-17.) The specification provides numerous examples of pharmaceutically acceptable carriers that may be included in the claimed compositions. The specification discloses that the carrier may be a "biocompatible pharmaceutical carrier, including, but not limited to, saline, buffered saline, dextrose, and water." (Page 44, lines 12-15.) The specification also discloses that pharmaceutically acceptable carriers include excipients. (Page 44, lines 16-19.) The specification discloses, "Suitable excipients are carbohydrate or protein fillers, such as sugars, including lactose, sucrose, mannitol, or sorbitol; starch from corn, wheat, rice, potato, or other plants; cellulose, such as methyl cellulose, hydroxypropylmethyl-cellulose, or sodium carboxymethylcellulose; gums including arabic and

tragacanth; and proteins such as gelatin and collagen." (Page 45, lines 2-6.) Thus the specification guides one of skill in the art as to what, other than an expression vector, would be included in a pharmaceutical composition. It would not require undue experimentation for one of skill in the art to make a pharmaceutical composition as recited in claims 62-64.

The Office Action concludes its rejection of claims 62-64 by stating, "Making and testing the infinite number of compositions to find one that is effective would constitute undue experimentation." (Paper 9, page 11, lines 16-17.) The Office Action, in requiring that pharmaceutical composition be clinically effective, has applied an incorrect standard for enablement. A therapeutic invention need not be refined to the point where clinical efficacy in patients can be demonstrated in order to be patentable. *In re Brana*, 51 F3d 1560 (Fed. Cir. 1995).

Withdrawal of this rejection to claims 62-64 is respectfully requested.

The Rejection of Claims 1, 6, 11, 27, and 69-71 Under 35 U.S.C. § 102 (b)

Claims 1, 6, 11, 27, and 69-71 stand rejected under 35 U.S.C. § 102 (b) as being anticipated by Hillier *et al.* (GenBank accession number R78581). The rejection is respectfully traversed.

To reject a claim as anticipated each and every element as set forth in the claim must be found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). See also MPEP § 2131.

Amended independent claims 1, 6, and 11 recite either a cDNA (claim 1), expression vector (claim 6), and host cell (claim 11) that encodes a polypeptide comprising an amino acid

sequence as shown in SEQ ID NO:12 or is encoded by a cDNA insert contained within plasmid pCRII-TMSP3 (ATCC Accession No. PTA-3433).

Hillier does not disclose a molecule that encodes either the amino acid sequence encoded by SEQ ID NO:12 or the amino acid sequence encoded by the insert of plasmid pCRII-TMSP3 (ATCC Accession No. PTA-3433). Hillier discloses a cDNA that comprises 151 contiguous nucleotides of a polynucleotide that encodes SEQ ID NO: 12. Hillier does not disclose a cDNA or polynucleotide molecule that encodes the full-length amino acid sequence of SEQ ID NO: 12 or the amino acid sequence encoded by the insert of plasmid pCRII-TMSP3 (ATCC Accession No. PTA-3433). See the alignment provided with the Office Action.

Claim 27 is directed to a kit. The kit comprises a polynucleotide that comprises at least 225 contiguous nucleotides of (a) a polynucleotide comprising the complete complement of the nucleotide sequence shown in SEQ ID NO: 11, (b) a polynucleotide comprising the complete complement of the coding sequence of the cDNA insert of plasmid pCRII-TMSP3 (ATCC Accession No. PTA-3433), (c) a polynucleotide that hybridizes under stringent conditions to (a) or (b), and (d) a polynucleotide having a nucleic acid sequence that deviates for the nucleic acid sequences specified in (a) – (c) due to the degeneration of the genetic code. The kit also includes instructions for detecting the coding sequence of the transmembrane serine protease. Hillier does not teach any of the polynucleotide molecules recited in claim 27 because Hillier does not teach at least 225 contiguous nucleotides of a polynucleotide sequence as recited in claim 27. Hillier teaches a 402-nucleotide sequence, of which a segment of only 151 nucleotides is identical to SEQ ID NO: 11. Hillier also does not expressly or inherently teach a kit or instructions for detecting the coding sequence of a transmembrane serine protease.

Claim 69 is directed to an isolated polynucleotide. The polynucleotides is (a) a polynucleotide encoding a protein that comprises the amino acid sequence of SEQ ID NO: 12, (b) a polynucleotide comprising the sequence of SEQ ID NO: 11, (c) a polynucleotide comprising a coding sequence of a cDNA contained within plasmid pCRII-TMSP3 (ATCC Accession No. PTA-3433), (d) a polynucleotide encoding a protein that comprises the amino acid sequence encoded by the cDNA of plasmid pCRII-TMSP3 (ATCC Accession No. PTA-3433), (e) a polynucleotide which hybridizes under condition along the full length of a polynucleotide specified in (a) – (d), or (f) a polynucleotide having a nucleic acid sequence that deviates from the nucleic acid sequences specified in (a) – (e) due to the degeneration of the genetic code.

Hillier also does not expressly or inherently teach any of these molecules. Again, Hillier teaches a cDNA that comprises only 151 contiguous nucleotides of a polynucleotide that encodes SEQ ID NO: 12. Thus, Hillier does not teach any of the polynucleotides recited in claim 69 and dependent claims 70-71.

Withdrawal of this rejection to claims 1, 6, 11, 27, and 69-71 is respectfully requested.

The Rejection of Claims 1, 6, 11, 27, and 69-71 Under 35 U.S.C. § 102 (b)

Claims 1, 6, 11, 27, and 69-71 stand rejected under 35 U.S.C. § 102 (b) as being anticipated by Paolini-Giacobino *et al.* (*Genomics*, *44*:309-320, 1997; EMBL accession number U75329, Swiss Prot accession number O15393). Applicants respectfully traverse.

Amended independent claims 1, 6, and 11 recite either a cDNA (claim 1), expression vector (claim 6), and host cell (claim 11) that encodes a polypeptide comprising an amino acid

sequence as shown in SEQ ID NO:12 or is encoded by a cDNA insert contained within plasmid pCRII-TMSP3 (ATCC Accession No. PTA-3433). Paolini-Giacobino does not expressly or inherently teach each and every element recited in claims 1, 6, and 11. Paolini-Giacobino teaches a 492 amino acid sequence that is 24.6% identical to SEQ ID NO:12. Thus Paolini-Giacobino does not teach a polynucleotide sequence that encodes a polypeptide comprising an amino acid sequence as shown in SEQ ID NO:12 or is encoded by a cDNA insert contained within plasmid pCRII-TMSP3 (ATCC Accession No. PTA-3433). See alignment provided with the Office Action.

Claim 27 is directed to a kit. The kit comprises a polynucleotide that comprises at least 225 contiguous nucleotides of (a) a polynucleotide comprising the complete complement of the nucleotide sequence shown in SEQ ID NO: 11, (b) a polynucleotide comprising the complete complement of the coding sequence of the cDNA insert of plasmid pCRII-TMSP3 (ATCC Accession No. PTA-3433), (c) a polynucleotide that hybridizes under stringent conditions to (a) or (b), and (d) a polynucleotide having a nucleic acid sequence that deviates for the nucleic acid sequences specified in (a) – (c) due to the degeneration of the genetic code. The kit also includes instructions for detecting the coding sequence of the transmembrane serine protease. Paolini-Giacobino does not teach any of the polynucleotide molecules recited in claim 27. Paolini-Giacobino teaches a 492 amino acid sequence that is 24.6% identical to SEQ ID NO:12. The longest stretch of contiguous nucleotides relative to SEQ ID NO: 11 is 12 nucleotides in length. Paolini-Giacobino also does not expressly or inherently teach a kit or instructions for detecting the coding sequence of a transmembrane serine protease.

Claim 69 is directed to an isolated polynucleotide. The polynucleotides is (a) a polynucleotide encoding a protein that comprises the amino acid sequence of SEQ ID NO: 12, (b) a polynucleotide comprising the sequence of SEQ ID NO: 11, (c) a polynucleotide comprising a coding sequence of a cDNA contained within plasmid pCRII-TMSP3 (ATCC Accession No. PTA-3433), (d) a polynucleotide encoding a protein that comprises the amino acid sequence encoded by the cDNA of plasmid pCRII-TMSP3 (ATCC Accession No. PTA-3433), (e) a polynucleotide which hybridizes under condition along the full length of a polynucleotide specified in (a) – (d), or (f) a polynucleotide having a nucleic acid sequence that deviates from the nucleic acid sequences specified in (a) – (e) due to the degeneration of the genetic code.

Paolini-Giacobino also does not expressly or inherently teach any of these molecules. Paolini-Giacobino teaches a 492 amino acid sequence that is 24.6% identical to SEQ ID NO:12. Thus Paolini-Giacobino does not teach the polynucleotides recited in claim 69, or dependent claims 70-71.

Withdrawal of this rejection of claims 1, 6, 11, 27, and 69-71 is respectfully requested.

The Rejection of Claim 22 Under 35 U.S.C. § 103 (a)

Claim 22 has been rejected under 35 U.S.C. § 103 (a) as being unpatentable over Hiller *et al.* (GenBank accession number R78581) or Paolini-Giacobino *et al.* (*Genomics*, *44*:309-320, 1997; EMBL accession number U75329; Swiss Prot accession number O15393). Applicants respectfully traverse.

The reject claims as *prima facie* obvious the Patent Office must meet three criteria:

> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

MPEP § 2143. The Patent Office has failed to meet the third criterion for making a *prima facie* case of obviousness.

Claim 22 is directed to a method of producing a polypeptide comprising either the amino acid sequence shown in SEQ ID NO:12 or the amino acid sequence encoded by a cDNA insert contained within plasmid pCRII-TMSP3 (ATCC Accession No. PTA-3433). The method is performed by culturing a host cell comprising an expression vector that encodes the polypeptide under conditions whereby the polypeptide is expressed. The polypeptide is isolated.

The Office Action cites Hillier and Paolini-Giacobino as teaching a cDNA that encodes a variant of SEQ ID NO:12 or an amino acid sequence that is a variant of SEQ ID NO:12, vectors comprising cDNA encoding the variants, and host cells comprising the vectors. (Paper 9, page 12, lines 4-9 and 14-21.) The Office Action asserts, "It would have been obvious to one of ordinary skill in the art at the time the invention was made to cultivate the host cell comprising the vectors, as taught by Hillier et al. or Paolini-Giacobino et al., for the benefit or producing the transmembrane serine proteases of Hillier or Paolini-Giacobino et al." (Paper 9, page 14, lines 6-9.) Neither of the transmembrane serine proteases of Hillier or Paolini-Giacobino, however, is a polypeptide recited in amended claim 22.

Hillier teaches a cDNA sequence that is identical to 151 nucleotides, or 50 amino acids of the coding sequence for SEQ ID NO:12. Paolini-Giacobino teaches a 492 amino acid sequence that is only 24.6% identical to SEQ ID NO:12. Thus neither Hillier nor Paolini-Giacobino teaches or suggests a polypeptide that comprises the amino acid sequence of SEQ ID NO: 12 or the amino acid sequence encoded by the cDNA insert contained within plasmid pCRII-TMSP3 (ATCC Accession No. PTA-3433) as recited in claim 22.

Withdrawal of this rejection to claim 22 is respectfully requested.

Respectfully submitted,

Dated: December 10, 2002

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Appendix I. Marked Up Version of the Amended Claims and Paragraphs to Show the Changes Made

CLAIMS

1. (Amended) A cDNA encoding a polypeptide comprising an amino acid sequence selected from the group consisting of (a) the amino acid sequence shown in SEQ ID NO:12~~,~~ **and** (b) the amino acid sequence encoded by a cDNA insert contained within plasmid pCRII-TMSP3 ~~(ATCC Accession No. _____)~~ **(ATCC Accession No. PTA-3433)** ~~, and (c) biologically active variants thereof~~.

6. (Amended) An expression vector comprising a polynucleotide which encodes a polypeptide comprising an amino acid sequence selected from the group consisting of (a) the amino acid sequence shown in SEQ ID NO:12~~,~~ **and** (b) the amino acid sequence encoded by a cDNA insert contained within plasmid pCRII-TMSP3 ~~(ATCC Accession No. _____)~~ **(ATCC Accession No. PTA-3433)** ~~, and (c) biologically active variants thereof~~.

11. (Amended) A host cell comprising an expression vector which encodes a polypeptide comprising an amino acid sequence selected from the group consisting of (a) the amino acid sequence shown in SEQ ID NO:12 ~~,~~ **and** (b) the amino acid sequence encoded by a cDNA insert contained within plasmid pCRII-TMSP3 ~~(ATCC Accession No. _____)~~ **(ATCC Accession No. PTA-3433)** ~~, and (c) biologically active variants thereof~~.

22. (Amended) A method of producing a polypeptide comprising an amino acid sequence selected from the group consisting of (a) the amino acid sequence shown in SEQ ID NO:12 ~~,~~ **and** (b) the amino acid sequence encoded by a cDNA insert contained within plasmid pCRII-TMSP3

~~(ATCC Accession No. _____)~~ **(ATCC Accession No. PTA-3433)**, ~~and (c) biologically active variants thereof,~~ comprising the steps of:

culturing a host cell comprising an expression vector that encodes the polypeptide under conditions whereby the polypeptide is expressed; and

isolating the polypeptide.

27. (Amended) A kit for detecting a coding sequence for a polypeptide comprising an amino acid sequence selected from the group consisting of (a) the amino acid sequence shown in SEQ ID NO:12 ; **and** (b) the amino acid sequence encoded by a cDNA insert contained within plasmid pCRII-TMSP3 ~~(ATCC Accession No. _____)~~ **(ATCC Accession No. PTA-3433)**, ~~and (c) biologically active variants thereof,~~ comprising:

a polynucleotide comprising ~~11~~ **at least 225** contiguous nucleotides selected from the group consisting of (a) **a polynucleotide comprising** the **complete** complement of the nucleotide sequence shown in SEQ ID NO:11, (b) **a polynucleotide comprising** the **complete** complement of the coding sequence of the cDNA insert of plasmid pCRII-TMSP3 **(ATCC Accession No. PTA-3433)** ~~to nucleic acid material of a biological sample to form a hybridization complex~~, (c) a polynucleotide that hybridizes under stringent conditions to (a) or (b), **and** (d) a polynucleotide having a nucleic acid sequence that deviates from the nucleic acid sequences specified in (a) to (c) due to the degeneration of the genetic code ~~, and (e) a polynucleotide that represents a fragment, derivative, or allelic variation of a nucleic acid sequence specified in (a) to (d)~~; and

instructions for ~~the method of claim 25~~ **detecting the coding sequence of the polypeptide**.

62. (Amended) A pharmaceutical composition, comprising:

an expression vector encoding a polypeptide comprising an amino acid sequence selected from the group consisting of (a) the amino acid sequence shown in SEQ ID NO:12 ; **and** (b) the amino acid sequence encoded by a cDNA insert contained within plasmid pCRII-TMSP3 ~~(ATCC Accession No. _____)~~ **(ATCC Accession No. PTA-3433)** ~~, and (c) biologically active variants thereof~~; and

a pharmaceutically acceptable carrier.

69. (Amended) An isolated polynucleotide selected from the group consisting of: (a) a polynucleotide encoding a protein that comprises the amino acid sequence of SEQ ID NO:12, (b) a polynucleotide comprising the sequence of SEQ ID NO:11, (c) a polynucleotide comprising a coding sequence of a cDNA contained within plasmid pCRII-TMSP3 ~~(ATCC Accession No. _____)~~ **(ATCC Accession No. PTA-3433)**, (d) a polynucleotide encoding a protein that comprises the amino acid sequence encoded by the cDNA of plasmid pCRII-TMSP3, (e) a polynucleotide which hybridizes under stringent conditions ~~to~~ **along the full length of** a polynucleotide specified in (a) - (d)~~;~~ **, and** ~~(e)~~ **(f)** a polynucleotide having a nucleic acid sequence that deviates from the nucleic acid sequences specified in (a) - ~~(d)~~ **(e)** due to the degeneration of the genetic code ~~, and (f) a polynucleotide that represents a fragment, derivative, or allelic variation of a nucleic acid sequence specified in (a) - (e)~~.

SPECIFICATION

The paragraph at page 1, lines 3-7.

This application claims the benefit of and incorporates by reference co-pending provisional applications Serial No. 60/211,224 filed June 13, 2000, Serial No. 60/283,353 filed April 13, 2001, and Serial No. 60/283,648 filed April 16, 2001, and PCT application ~~_____~~ **PCT/EP01/06618** filed June 12, 2001 ~~under Attorney Docket No. LIO-81-WO~~.

The paragraph at page 2, lines 9-13.

One embodiment of the invention is a cDNA encoding a polypeptide comprising an amino acid sequence selected from the group consisting of (a) the amino acid sequence shown in SEQ ID NO:12, (b) the amino acid sequence encoded by a cDNA insert contained within plasmid pCRII-TMSP3 ~~(ATCC Accession No. _____)~~ **(ATCC Accession No. PTA-3433)**, and (c) biologically active variants thereof.

The paragraph at page 2, lines 14-19.

Yet another embodiment of the invention is an expression vector comprising a polynucleotide which encodes a polypeptide comprising an amino acid sequence selected from the group consisting of (a) the amino acid sequence shown in SEQ ID NO:12, (b) the amino acid sequence encoded by a cDNA insert contained within plasmid pCRII-TMSP3 ~~(ATCC Accession No. _____)~~ **(ATCC Accession No. PTA-3433)**, and (c) biologically active variants thereof.

The paragraph at page 2, lines 20-24.

Another embodiment of the invention is a host cell comprising an expression vector which encodes a polypeptide comprising an amino acid sequence selected from the group

consisting of (a) the amino acid sequence shown in SEQ ID NO:12, (b) the amino acid sequence encoded by a cDNA insert contained within plasmid pCRII-TMSP3 ~~(ATCC Accession No. _____)~~ **(ATCC Accession No. PTA-3433)**, and (c) biologically active variants thereof.

The paragraph at page 2, lines 25-29.

Still another embodiment of the invention is a purified polypeptide comprising an amino acid sequence selected from the group consisting of (a) the amino acid sequence shown in SEQ ID NO:12, (b) the amino acid sequence encoded by a cDNA insert contained within plasmid pCRII-TMSP3 ~~(ATCC Accession No. _____)~~ **(ATCC Accession No. PTA-3433)**, and (c) biologically active variants thereof.

The paragraph at page 3, lines 1-5.

Even another embodiment of the invention is a fusion protein comprising a polypeptide consisting of an amino acid sequence selected from the group consisting of (a) the amino acid sequence shown in SEQ ID NO:12, (b) the amino acid sequence encoded by a cDNA insert contained within plasmid pCRII-TMSP3 ~~(ATCC Accession No. _____)~~ **(ATCC Accession No. PTA-3433)**, and (c) biologically active variants thereof.

The paragraph at page 3, lines 6-12.

Another embodiment of the invention is a method of producing a polypeptide comprising an amino acid sequence selected from the group consisting of (a) the amino acid sequence shown in SEQ ID NO:12, (b) the amino acid sequence encoded by a cDNA insert contained within plasmid pCRII-TMSP3 ~~(ATCC Accession No. _____)~~ **(ATCC Accession No. PTA-3433)**, and (c) biologically active variants thereof. A host cell comprising an expression vector that

encodes the polypeptide is cultured under conditions whereby the polypeptide is expressed. The polypeptide is isolated.

The paragraph at page 3, lines 13-26.

Yet another embodiment of the invention is a method of detecting a coding sequence for a polypeptide comprising an amino acid sequence selected from the group consisting of (a) the amino acid sequence shown in SEQ ID NO:12, (b) the amino acid sequence encoded by a cDNA insert contained within plasmid pCRII-TMSP3 ~~(ATCC Accession No. _____)~~ **(ATCC Accession No. PTA-3433)**, and (c) biologically active variants thereof. A polynucleotide comprising 11 contiguous nucleotides selected from the group consisting of (a) the complement of the nucleotide sequence shown in SEQ ID NO:11, (b) the complement of the coding sequence of the cDNA insert of plasmid pCRII-TMSP3, (c) a polynucleotide that hybridizes under stringent conditions to (a) or (b), (d) a polynucleotide having a nucleic acid sequence that deviates from the nucleic acid sequences specified in (a) to (c) due to the degeneration of the genetic code, and (e) a polynucleotide that represents a fragment, derivative, or allelic variation of a nucleic acid sequence specified in (a) to (d) is hybridized to nucleic acid material of a biological sample to form a hybridization complex. The hybridization complex is detected.

The paragraph at page 3, line 27 to page 4, line 12.

Even another embodiment of the invention is a kit for detecting a coding sequence for a polypeptide comprising an amino acid sequence selected from the group consisting of (a) the amino acid sequence shown in SEQ ID NO:12, (b) the amino acid sequence encoded by a cDNA insert contained within plasmid pCRII-TMSP3 ~~(ATCC Accession No. _____)~~ **(ATCC Accession N . PTA-3433)**, and (c) biologically active variants thereof. The kit comprises a

polynucleotide and instructions for detecting the coding sequence. The polynucleotide comprises 11 contiguous nucleotides selected from the group consisting of (a) the complement of the nucleotide sequence shown in SEQ ID NO:11, (b) the complement of the coding sequence of the cDNA insert of plasmid pCRII-TMSP3 to nucleic acid material of a biological sample to form a hybridization complex, (c) a polynucleotide that hybridizes under stringent conditions to (a) or (b), (d) a polynucleotide having a nucleic acid sequence that deviates from the nucleic acid sequences specified in (a) to (c) due to the degeneration of the genetic code, and (e) a polynucleotide that represents a fragment, derivative, or allelic variation of a nucleic acid sequence specified in (a) to (d).

The paragraph at page 4, lines 13-19.

Still another embodiment of the invention is a method of detecting a polypeptide comprising an amino acid sequence selected from the group consisting of (a) the amino acid sequence shown in SEQ ID NO:12, (b) the amino acid sequence encoded by a cDNA insert contained within plasmid pCRII-TMSP3 ~~(ATCC Accession No. _____)~~ **(ATCC Accession No. PTA-3433)**, and (c) biologically active variants thereof. A biological sample is contacted with a reagent that specifically binds to the polypeptide to form a reagent-polypeptide complex. The reagent-polypeptide complex is detected.

The paragraph at page 4, lines 20-25.

Yet another embodiment of the invention is a kit for detecting a polypeptide comprising an amino acid sequence selected from the group consisting of (a) the amino acid sequence shown in SEQ ID NO:12, (b) the amino acid sequence encoded by a cDNA insert contained within plasmid pCRII-TMSP3 ~~(ATCC Accession No. _____)~~ **(ATCC Accession No. PTA-3433)**,

and (c) biologically active variants thereof. The kit comprises an antibody which specifically binds to the polypeptide and instructions for detecting the polypeptide.

The paragraph at page 4, lines 26 to page 5, line 5.

Even another embodiment of the invention is a method of screening for agents that can regulate an activity of a human transmembrane serine protease. A test compound is contacted with a polypeptide comprising an amino acid sequence selected from the group consisting of: (a) the amino acid sequence shown in SEQ ID NO:12, (b) the amino acid sequence encoded by a cDNA insert contained within plasmid pCRII-TMSP3 ~~(ATCC Accession No. _____)~~ **(ATCC Accession No. PTA-3433)**, and (c) biologically active variants thereof. Binding of the test compound to the polypeptide is detected. A test compound that binds to the polypeptide is thereby identified as a potential agent for regulating the activity of the human transmembrane serine protease.

The paragraph at page 5, lines 6-17.

A further embodiment of the invention is a method of screening for therapeutic agents that can regulate an enzymatic activity of a human transmembrane serine protease. A test compound is contacted with a polypeptide comprising an amino acid sequence selected from the group consisting of: (a) the amino acid sequence shown in SEQ ID NO:12, (b) the amino acid sequence encoded by a cDNA insert contained within plasmid pCRII-TMSP3 ~~(ATCC Accession No. _____)~~ **(ATCC Accession No. PTA-3433)**, and (c) biologically active variants thereof. The enzymatic activity of the polypeptide is detected. A test compound that increases the enzymatic activity of the polypeptide is thereby identified as a potential therapeutic agent for increasing the enzymatic activity of the human transmembrane serine protease. A test compound

that decreases the enzymatic activity of the polypeptide is thereby identified as a potential therapeutic agent for decreasing the enzymatic activity of the human transmembrane serine protease.

The paragraph at page 5, lines 18-27.

Still another embodiment of the invention is a method of screening for therapeutic agents that can regulate an activity of a human transmembrane serine protease. A test compound is contacted with a product encoded by a polynucleotide comprising a nucleotide sequence selected from the group consisting of (a) the amino acid sequence shown in SEQ ID NO:12, (b) the amino acid sequence encoded by a cDNA insert contained within plasmid pCRII-TMSP3 ~~(ATCC Accession No. _____)~~ **(ATCC Accession No. PTA-3433)**, and (c) biologically active variants thereof. Binding of the test compound to the product is detected. A test compound that binds to the product is thereby identified as a potential therapeutic agent for regulating the activity of the human transmembrane serine protease.

The paragraph at page 5, line 28 to page 6, line 6.

Another embodiment of the invention is a method of reducing an activity of a human transmembrane serine protease. A cell comprising the human transmembrane serine protease is contacted with a reagent that specifically binds to a product encoded by a polynucleotide comprising a nucleotide sequence selected from the group consisting of (a) the amino acid sequence shown in SEQ ID NO:12, (b) the amino acid sequence encoded by a cDNA insert contained within plasmid pCRII-TMSP3 ~~(ATCC Accession No. _____)~~ **(ATCC Accession No. PTA-3433)**, and (c) biologically active variants thereof. The activity of the human transmembrane serine protease is thereby reduced.

The paragraph at page 6, lines 7-12.

Yet another embodiment of the invention is a pharmaceutical composition, comprising a reagent and a pharmaceutically acceptable carrier. The reagent specifically binds to a polypeptide comprising an amino acid sequence selected from the group consisting of (a) the amino acid sequence shown in SEQ ID NO:12, (b) the amino acid sequence encoded by a cDNA insert contained within plasmid pCRII-TMSP3 ~~(ATCC Accession No. _____)~~ **(ATCC Accession No. PTA-3433)**, and (c) biologically active variants thereof; and

The paragraph at page 6, lines 13-19.

Even another embodiment of the invention is a pharmaceutical composition comprising a reagent and a pharmaceutically acceptable carrier. The reagent specifically binds to a product of a polynucleotide comprising a coding sequence selected from the group consisting of (a) the amino acid sequence shown in SEQ ID NO:12, (b) the amino acid sequence encoded by a cDNA insert contained within plasmid pCRII-TMSP3 ~~(ATCC Accession No. _____)~~ **(ATCC Accession No. PTA-3433)**, and (c) biologically active variants thereof.

The paragraph at page 6, lines 20-25.

A further embodiment of the invention is a pharmaceutical composition comprising an expression vector and a pharmaceutically acceptable carrier. The expression vector encodes a polypeptide comprising an amino acid sequence selected from the group consisting of (a) the amino acid sequence shown in SEQ ID NO:12, (b) the amino acid sequence encoded by a cDNA insert contained within plasmid pCRII-TMSP3 ~~(ATCC Accession No. _____)~~ **(ATCC Accession No. PTA-3433)**, and (c) biologically active variants thereof.

The paragraph at page 6, line 26 to page 7, line 7.

Still another embodiment of the invention is a method of treating a disorder selected from the group consisting of chronic obstructive pulmonary disease, cancer, metastasis of malignant cells, tumor angiogenesis, inflammation, atherosclerosis, neurodegenerative diseases, and pathogenic infections. A therapeutically effective dose of a reagent that inhibits a function of a human transmembrane serine protease is administered to a patient in need thereof. The human transmembrane serine protease comprises an amino acid sequence selected from the group consisting of (a) the amino acid sequence shown in SEQ ID NO:12, (b) the amino acid sequence encoded by a cDNA insert contained within plasmid pCRII-TMSP3 ~~(ATCC Accession No. _____)~~ **(ATCC Accession No. PTA-3433)**, and (c) biologically active variants thereof. Symptoms of the disorder are thereby ameliorated.

The paragraph at page 7, lines 8-19.

Even another embodiment of the invention is a isolated polynucleotide selected from the group consisting of: (a) a polynucleotide encoding a protein that comprises the amino acid sequence of SEQ ID NO:12, (b) a polynucleotide comprising the sequence of SEQ ID NO:11, (c) a polynucleotide comprising a coding sequence of a cDNA contained within plasmid pCRII-TMSP3 ~~(ATCC Accession No. _____)~~ **(ATCC Accession No. PTA-3433)**, (d) a polynucleotide encoding a protein that comprises the amino acid sequence encoded by the cDNA of plasmid pCRII-TMSP3, (e) a polynucleotide which hybridizes under stringent conditions to a polynucleotide specified in (a) - (d); (e) a polynucleotide having a nucleic acid sequence that deviates from the nucleic acid sequences specified in (a) - (d) due to the degeneration of the

genetic code, and (f) a polynucleotide that represents a fragment, derivative, or allelic variation of a nucleic acid sequence specified in (a) - (e).

The paragraph at page 7, line 20 to page 8, line 2.

Yet another embodiment of the invention is an expression vector comprising polynucleotide selected from the group consisting of: (a) a polynucleotide encoding a protein that comprises the amino acid sequence of SEQ ID NO:12, (b) a polynucleotide comprising the sequence of SEQ ID NO:11, (c) a polynucleotide comprising a coding sequence of a cDNA contained within plasmid pCRII-TMSP3 ~~(ATCC Accession No. _____)~~ **(ATCC Accession No. PTA-3433)**, (d) a polynucleotide encoding a protein that comprises the amino acid sequence encoded by the cDNA of plasmid pCRII-TMSP3, (e) a polynucleotide which hybridizes under stringent conditions to a polynucleotide specified in (a) - (d); (e) a polynucleotide having a nucleic acid sequence that deviates from the nucleic acid sequences specified in (a) - (d) due to the degeneration of the genetic code, and (f) a polynucleotide that represents a fragment, derivative, or allelic variation of a nucleic acid sequence specified in (a) - (e).

The paragraph at page 8, lines 3-14.

A further embodiment of the invention is a host cell comprising an expression vector comprising polynucleotide selected from the group consisting of: (a) a polynucleotide encoding a protein that comprises the amino acid sequence of SEQ ID NO:12, (b) a polynucleotide comprising the sequence of SEQ ID NO:11, (c) a polynucleotide comprising a coding sequence of a cDNA contained within plasmid pCRII-TMSP3 ~~(ATCC Accession No. _____)~~ **(ATCC Accession No. PTA-3433)**, (d) a polynucleotide encoding a protein that comprises the amino acid sequence encoded by the cDNA of plasmid pCRII-TMSP3, (e) a polynucleotide which

hybridizes under stringent conditions to a polynucleotide specified in (a) - (d); (e) a polynucleotide having a nucleic acid sequence that deviates from the nucleic acid sequences specified in (a) - (d) due to the degeneration of the genetic code, and (f) a polynucleotide that represents a fragment, derivative, or allelic variation of a nucleic acid sequence specified in (a) - (e).

The paragraph at page 8, lines 15-19.

Another embodiment of the invention is a preparation of antibodies that specifically bind to a polypeptide selected from the group consisting of (a) the amino acid sequence shown in SEQ ID NO:12, (b) the amino acid sequence encoded by a cDNA insert contained within plasmid pCRII-TMSP3 ~~(ATCC Accession No. _____)~~ **(ATCC Accession No. PTA-3433)**, and (c) biologically active variants thereof.

The paragraph at page 8, line 20 to page 9, line 2.

Even another embodiment of the invention is a antisense oligonucleotide that hybridizes to a polynucleotide selected from the group consisting of (a) a polynucleotide encoding a protein that comprises the amino acid sequence of SEQ ID NO:12, (b) a polynucleotide comprising the sequence of SEQ ID NO:11, (c) a polynucleotide comprising a coding sequence of a cDNA contained within plasmid pCRII-TMSP3 ~~(ATCC Accession No. _____)~~ **(ATCC Accession No. PTA-3433)**, (d) a polynucleotide encoding a protein that comprises the amino acid sequence encoded by the cDNA of plasmid pCRII-TMSP3, (e) a polynucleotide which hybridizes under stringent conditions to a polynucleotide specified in (a) - (d); (e) a polynucleotide having a nucleic acid sequence that deviates from the nucleic acid sequences specified in (a) - (d) due to

the degeneration of the genetic code, and (f) a polynucleotide that represents a fragment, derivative, or allelic variation of a nucleic acid sequence specified in (a) - (e).

FIG. 1

BLASTP - query = 147_TR1; Hit = swiss|O15393|TMS2_HUMAN

This hit is scoring at : 3e-66 (expectation value)
Alignment length (overlap) : 370
Identities : 38 %
Scoring matrix : BLOSUM62 (used to infer consensus pattern)
Database searched : nrdb

```
Q:     36 CDGVVDCKLKSDELGCVRFDWDKSLLKIYSGSSHQWLPICSSNWNDSYSEKTCQQLGFES
          CDGV .C.  .DE  CVR.  . . :L:.YS.....W P:C..:WN::Y....C:.:G:::
H:    133 CDGVSHCPGGEDENRCVRLYGPNFILQMYSSQRKSWHPVCQDDWNENYGRAACRDMGYKN

          AHRTTEVAHRDFANSFSILRYNST      IQESLHRSE CPSQRYISLQCSHCGLRA
           . :::.  D :.S S.:.N::       I..L:.S: C.S:..:SL:C  CG:.  :
          NFYSSQGIVDD SGSTSFMKLNTSAGNVDIYKKLYHSDACSSKAVVSLRCLACGVNLNSS

          MTGRIVGGALASDSKWPWQVSLHFGTTHICGGTLIDAQWVLTAAHCFFVTREKVLEG---
          ...RIVGG. A ...WPWQVSLH. ..H:CGG::I..:W::TAAHC.     EK L..
          RQSRIVGGESALPGAWPWQVSLHVQNVHVCGGSIITPEWVTAAHCV     EKPLNNPWH
                                                  TRYPSIN HIS
          WKVYAGTSNLHQLPEAAS--IAEIIINSNYTDEEDDYDIALMRLSKPLTLSGEGICTP
          W..:AG. . . :  .A.  :.::I :.NY.....: DIALM:L.KPLT.:.  : :C.P
          WTAFAGILRQSFMFYGAGYQVQKVISHPNYDSKTKNNDIALMKLQKPLTFNDLVKPVCLP

          RSPAPQPQHPLQPSHLSASVNSYPGPKASADKTSPFLREVQVNLIDFKKCNDYLVYDSYL
          .     P   LQP..L . :.:. G.....KTS..L...:V L1: ::CN. .VYD:.:
          N     PGMMLQPEQL-CWISGWGATEEKGKTSEVLNAAKVLLIETQRCNSRYVYDNLI

          TPRMMCAGDLRGGRDSCQGDSGGPLVCEQNNRWYLAGVTSWGTGCGQRNKPGVYTKVTEV
          TP.M:CAG L:G. DSCQGDSGGPLV...NN W:L.G TSWG:GC.:. :PGVY .V..
          TPAMICAGFLQGNVDSCQGDSGGPLVTSNNNIWWLIGDTSWGSGCAKAYRPGVYGNVMVF
                             TRYPSIN_SER
          LPWIYSKMEA     389
          ..WIY.:M:A
          TDWIYRQMKA     490
```

FIG. 2

Prosite search results

PS00134	187->193	TRYPSIN_HIS	PDOC00124
PS00135	334->346	TRYPSIN_SER	PDOC00124

FIG. 3

BLOCKS search results

AC#	Description	Strength	Score
BL00495N	Apple domain proteins.	1945	1582
AA#	325 AGdlrGGrDsCqGDSGGPLVCeqNnRWyLaGvTSW (SEQ ID NO:15)		
BL01253G	Type I fibronectin domain proteins.	1641	1548
AA#	332 rDsCQGDSGGPLVC (SEQ ID NO:16)		
BL00134A	Serine proteases, trypsin family, histidine p	1500	1524
AA#	175 CGGTLIDAQWVLTAAHC (SEQ ID NO:17)		
BL00021D	Kringle domain proteins.	1556	1510
AA#	341 GPLVCEQNNRWYLaGVTSWGtGCGQRNKPGVYTKVTevLPWI (SEQ ID NO:18)		
BL01253H	Type I fibronectin domain proteins.	1765	1508
AA#	351 wYLaGvtSWGtGCGQRNKPGVYTKVTevLpWIysk (SEQ ID NO:19)		
BL00021B	Kringle domain proteins.	1547	1507
AA#	175 CGGTLIDaQWVLTAAHCF (SEQ ID NO:20)		
BL00495O	Apple domain proteins.	1756	1383
AA#	360 GtGCGQRnkPGVYTKVtEvlpWIysKmeA (SEQ ID NO:21)		
BL00134B	Serine proteases, trypsin family, histidine p	1289	1299
AA#	333 DSCQGDSGGPLVCEqNNRWYLAGV (SEQ ID NO:22)		
BL01209	LDL-receptor class A (LDLRA) domain proteins.	1413	1274
AA#	35 CDGVVDCKlKSDE (SEQ ID NO:23)		
BL01253F	Type I fibronectin domain proteins.	1693	1270
AA#	288 AdktSpFLREvQVnLidfkKCndylVYdSylTPrMmCAG (SEQ ID NO:24)		
BL00495L	Apple domain proteins.	1947	1263
AA#	209 tSnlhqlpeaaSIaEIIInsNYtdeEddYDIALmrLskP (SEQ ID NO:25)		
BL00134C	Serine proteases, trypsin family, histidine p	1245	1254
AA#	369 PGVYTKVTEVLPWI (SEQ ID NO:26)		
BL01253D	Type I fibronectin domain proteins.	1398	1217
AA#	175 CGGtLIdaqWVLTA (SEQ ID NO:27)		

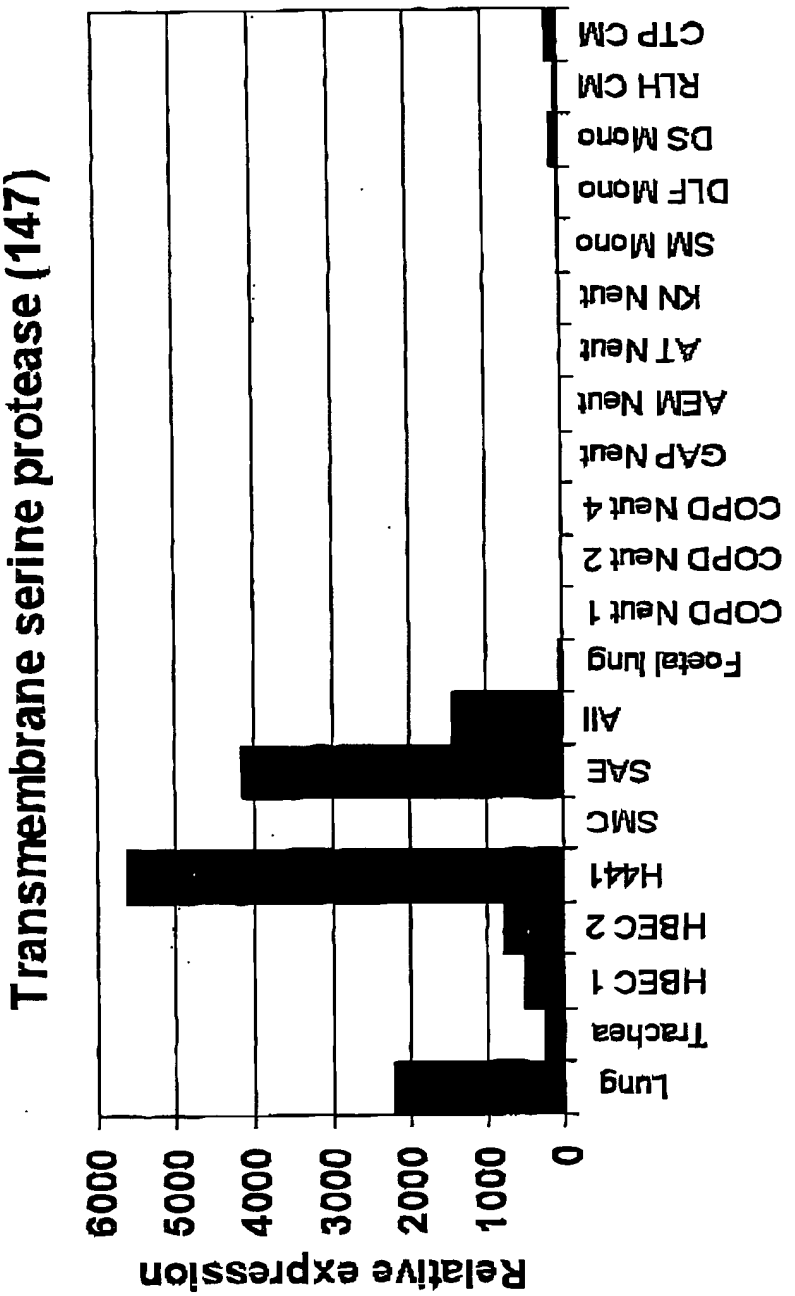
Transmembrane serine protease (147)
Relative expression
0
1000
2000
3000
4000
5000
6000
Lung
Trachea
HBEC 1
HBEC 2
H441
SMC
SAE
All
Foetal lung
COPD Neut 1
COPD Neut 2
COPD Neut 4
GAP Neut
AEM Neut
AT Neut
KN Neut
SM Mono
DLF Mono
DS Mono
RLH CM
CTP CM

FIG. 4

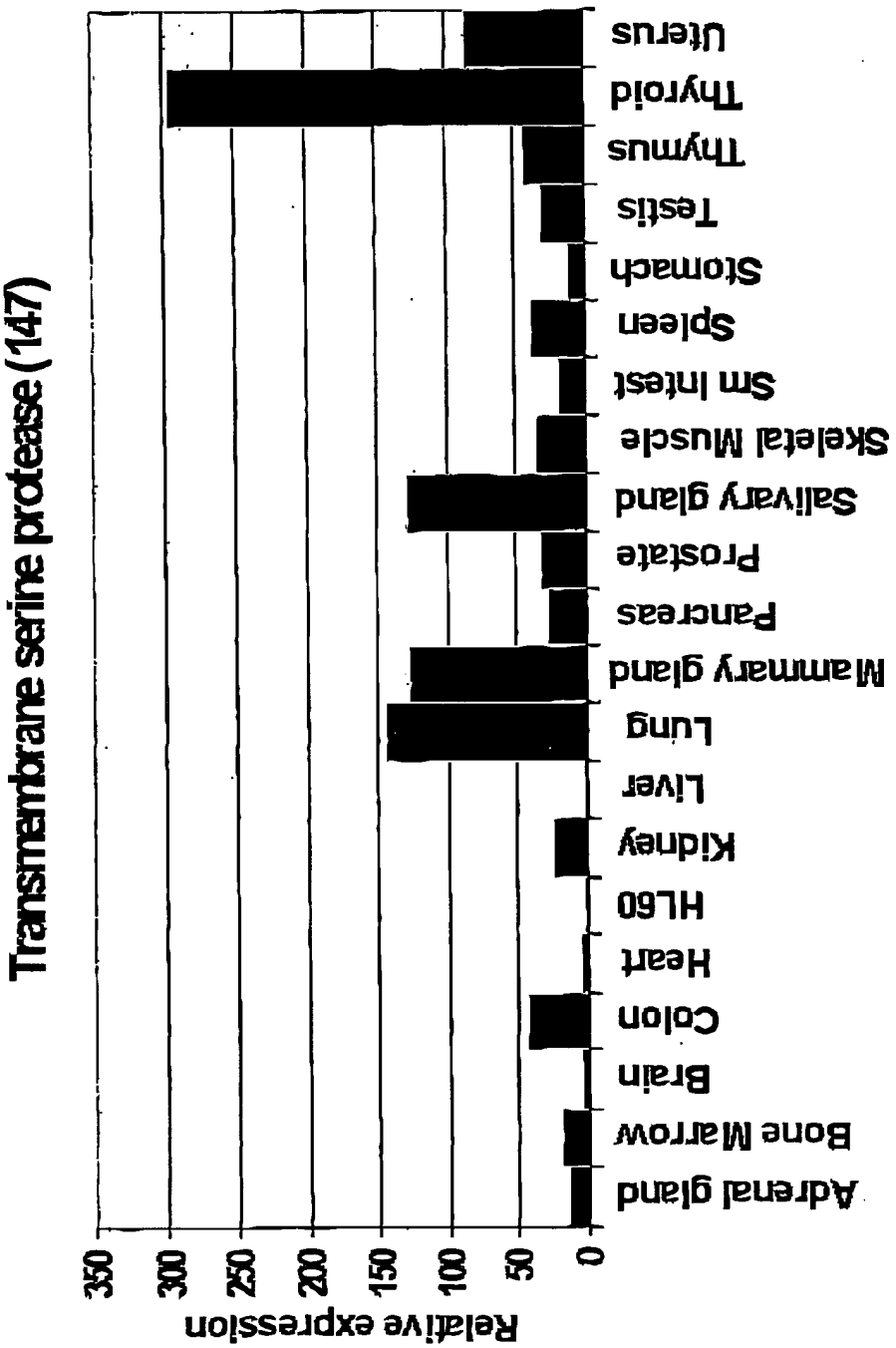
Transmembrane serine protease (147)
Relative expression
350
300
250
200
150
100
50
0
Adrenal gland
Bone Marrow
Brain
Colon
Heart
HL60
Kidney
Liver
Lung
Mammary gland
Pancreas
Prostate
Salivary gland
Skeletal Muscle
Sm Intest
Spleen
Stomach
Testis
Thymus
Thyroid
Uterus

FIG. 5

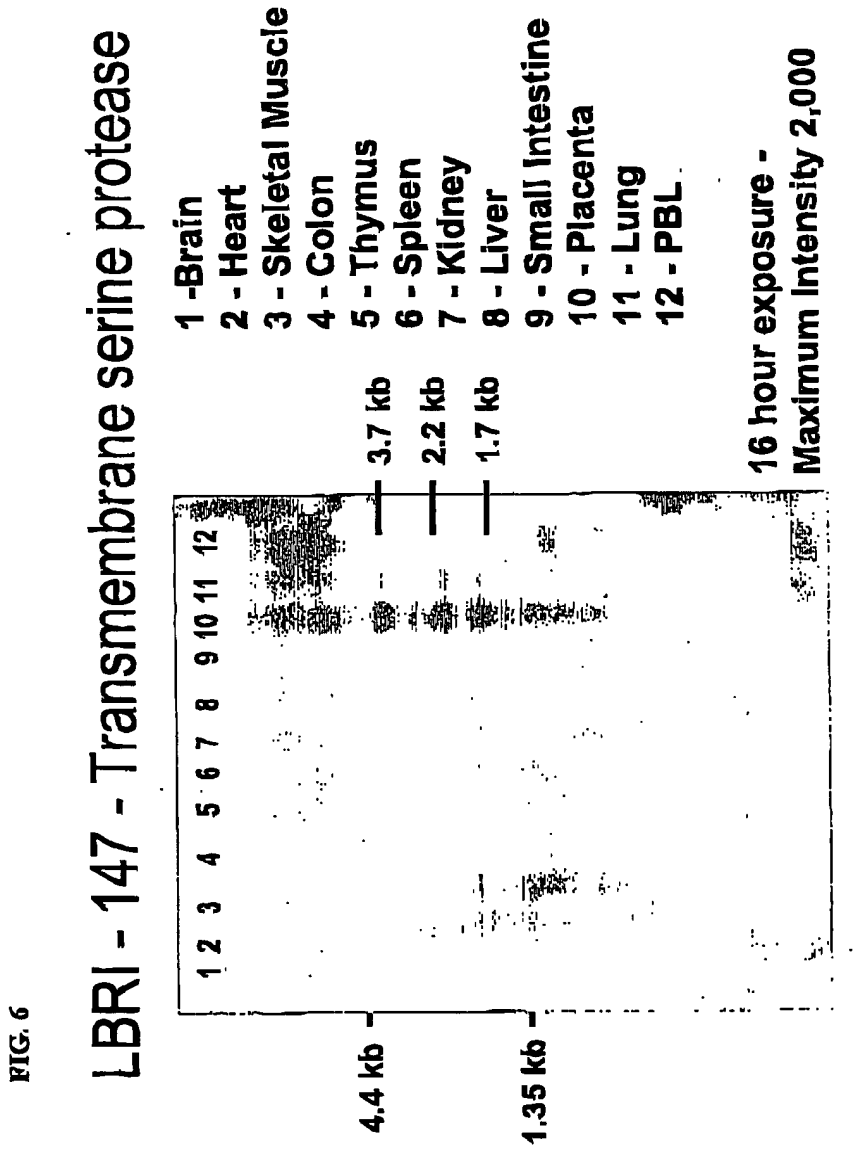
LBRI - 147 - Transmembrane serine protease
1 -Brain
2 - Heart
3 - Skeletal Muscle
4 - Colon
5 - Thymus
6 - Spleen
7 - Kidney
8 - Liver
9 - Small Intestine
10 - Placenta
11 - Lung
12 - PBL
16 hour exposure -
Maximum Intensity 2,000
1 2 3 4 5 6 7 8 9 10 11 12
3.7 kb
2.2 kb
1.7 kb
4.4 kb
1.35 kb

FIG. 6

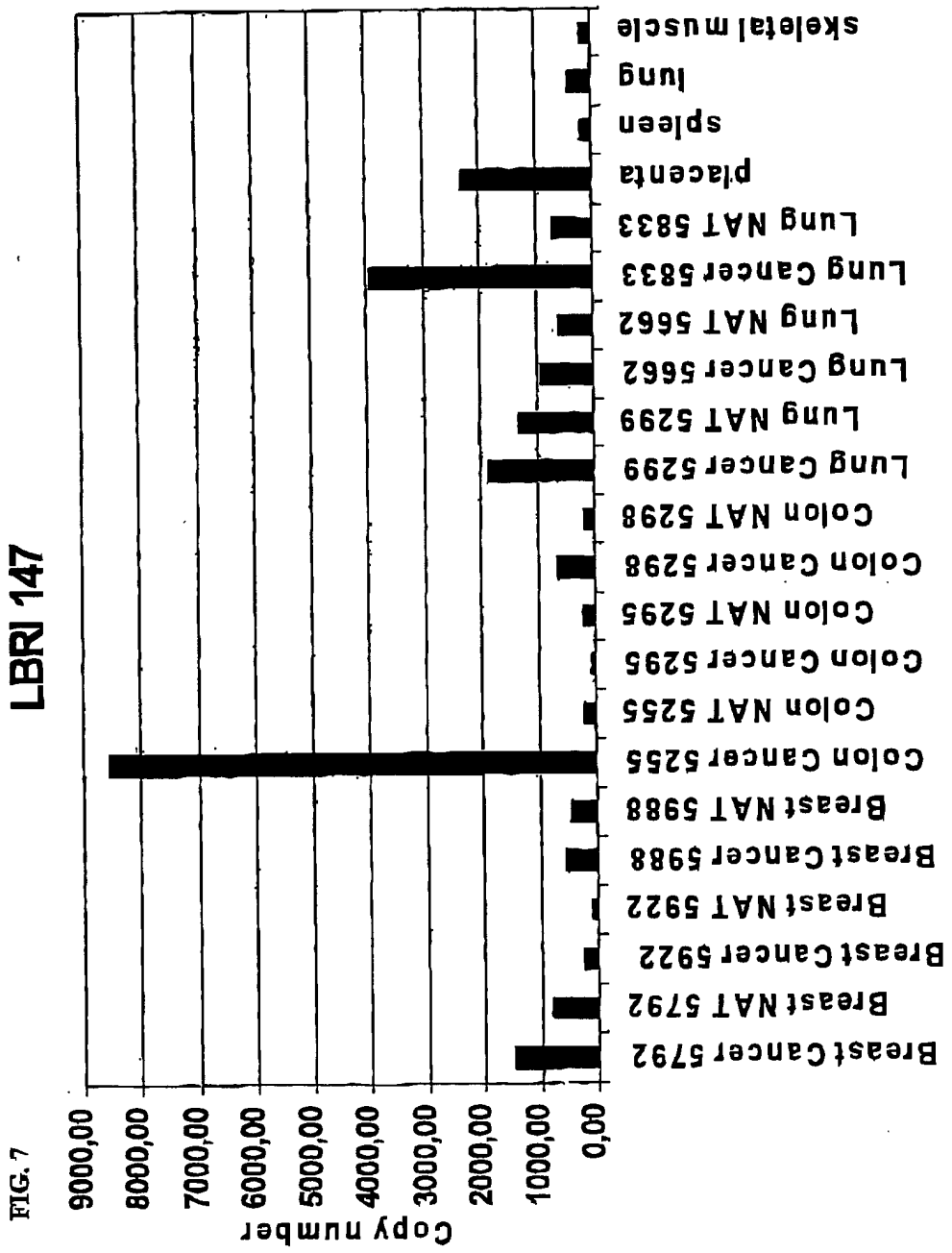
LBRI 147
Copy number
9000,00
8000,00
7000,00
6000,00
5000,00
4000,00
3000,00
2000,00
1000,00
0,00
Breast Cancer 5792
Breast NAT 5792
Breast Cancer 5922
Breast NAT 5922
Breast Cancer 5988
Breast NAT 5988
Colon Cancer 5255
Colon NAT 5255
Colon Cancer 5295
Colon NAT 5295
Colon Cancer 5298
Colon NAT 5298
Lung Cancer 5299
Lung NAT 5299
Lung Cancer 5662
Lung NAT 5662
Lung Cancer 5833
Lung NAT 5833
placenta
spleen
lung
skeletal muscle

FIG. 7

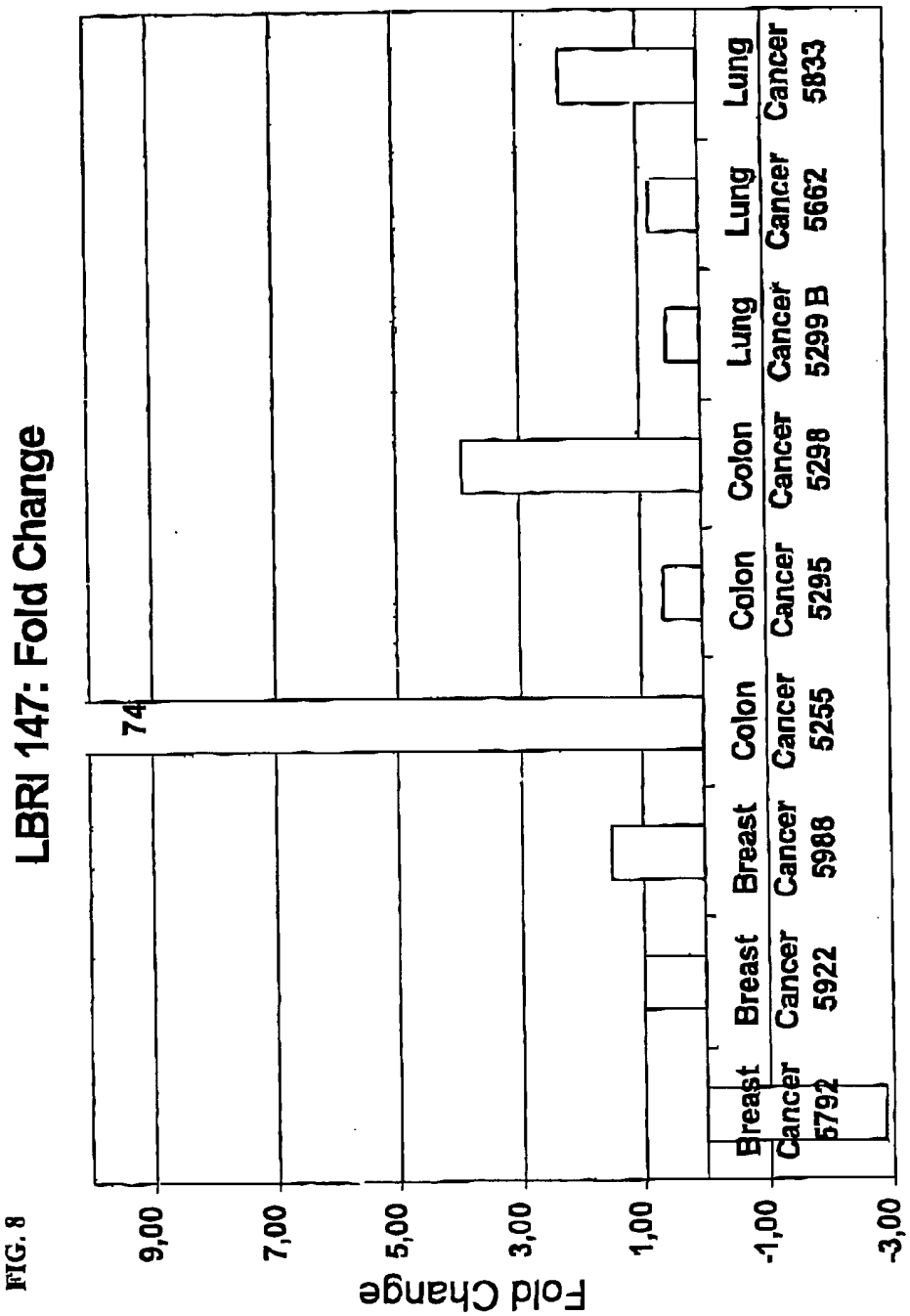
LBRI 147: Fold Change
Fold Change
9,00
7,00
5,00
3,00
1,00
-1,00
-3,00
74
Breast Cancer 5792
Breast Cancer 5922
Breast Cancer 5988
Colon Cancer 5255
Colon Cancer 5295
Colon Cancer 5298
Lung Cancer 5299 B
Lung Cancer 5662
Lung Cancer 5833

FIG. 8

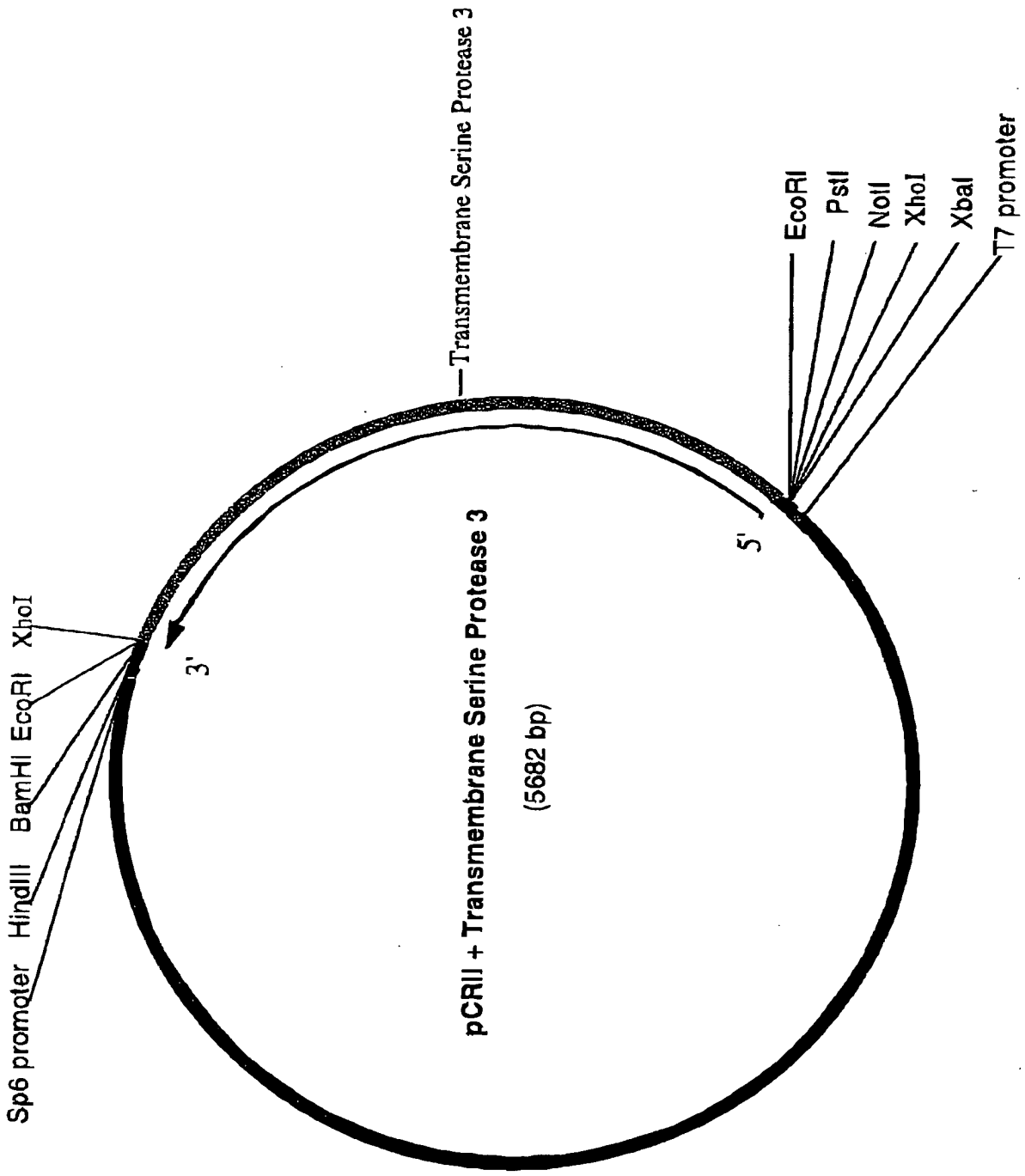
Transmembrane Serine Protease 3
EcoRI
PstI
NotI
XhoI
XbaI
T7 promoter
5'
3'
pCRII + Transmembrane Serine Protease 3
(5682 bp)
Sp6 promoter
HindIII
BamHI
EcoRI
XhoI

FIG. 9

ATCC

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BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF
THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

INTERNATIONAL FORM

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT ISSUED PURSUANT TO RULE 7.3
AND VIABILITY STATEMENT ISSUED PURSUANT TO RULE 10.2

To: (Name and Address of Depositor or Attorney)

Bayer Corporation
Attn; Richard W. Gedrich
400 Morgan Lane
West Haven, CT 06516

Deposited on Behalf of: Bayer AG and Bayer Corporation

Identification Reference by Depositor: **Patent Deposit Designation**

Plasmid pCRII containing a 1745 base pair cDNA encoding
human Transmembrane Serine Protease 3 (TMSP3): pCRII-TMSP3 PTA-3433

The deposit was accompanied by: __ a scientific description __ a proposed taxonomic description indicated above.

The deposit was received June 7, 2001 by this International Depository Authority and has been accepted.

AT YOUR REQUEST: X We will inform you of requests for the strain for 30 years.

The strain will be made available if a patent office signatory to the Budapest Treaty certifies one's right to receive, or if a U.S. Patent is issued citing the strain, and ATCC is instructed by the United States Patent & Trademark Office or the depositor to release said strain.

If the culture should die or be destroyed during the effective term of the deposit, it shall be your responsibility to replace it with living culture of the same.

The strain will be maintained for a period of at least 30 years from date of deposit, or five years after the most recent request for a sample, whichever is longer. The United States and many other countries are signatory to the Budapest Treaty.

The viability of the culture cited above was tested June 13, 2001. On that date, the culture was viable.

International Depository Authority: American Type Culture Collection, Manassas, VA 20110-2209 USA.

Signature of person having authority to represent ATCC:

Tanya Nunnally, Patent Specialist, Patent Depository **Date:** June 28, 2001

cc: Lisa Hemmendinger
(Ref: Docket or Case No.: 4974.00037)

** TOTAL PAGE.002 **